Expression of c-kit in Adenoid Cystic Carcinoma and Polymorphous Adenocarcinoma

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ABSTRACT

Introduction: Adenoid cystic carcinoma (ACC) and polymorphous adenocarcinoma (PAC) are salivary gland malignancies with some overlapping histomorphologic feature and immunophenotypic profiles; however their biologic behavior is significantly different. Study aimed to evaluate and compare the immunohistochemical expression of C-Kit (CD117) in differentiating adenoid cystic carcinoma and polymorphous adenocarcinoma.

Material and methods: A retrospective study was conducted on 20 formalin-fixed, paraffin-embedded tissue blocks, including 15 cases of Adenoid Cystic Carcinoma (5 cases for each pattern) and 5 cases of Polymorphous Adenocarcinoma histopathologically diagnosed using hematoxylin and eosin. All the sections were stained immunohistochemically using C-Kit.

Results: In the present study, a significant increase in C-Kit expression (both percentage of C-Kit stained cells and intensity of C-Kit) in adenoid cystic carcinoma as compared to polymorphous adenocarcinoma

Conclusion: Thus, the percentage of the C-kit immunoreactive cells and the staining intensities are considered to be an important factor in distinguishing adenoid cystic carcinoma from polymorphous adenocarcinoma.

Keywords: Staining Intensity, C-Kit, Immunohistochemistry, Salivary Gland Neoplasm

INTRODUCTION

Salivary glands have the histologically heterogeneous group of tumours and greatest diversity of morphological features amongst their cells and tissue. Even though their characteristically rather pronounced variation in histological appearance, all salivary gland tumours were simplistically separated only into infiltrating and encapsulated type. The morphology of salivary gland tumor reveals the cellular make up of basic ductoacinar unit of normal salivary gland. Adenoid cystic carcinoma (ACC) and polymorphous adenocarcinoma (PAC) are salivary gland malignancies with some overlapping histomorphologic features and immunophenotypic profiles; however their biologic behavior is considerably diverse. Some histopathologic resemblance is predictable as both tumours are believed to originate from intercalated duct as well as consisted of ductal and abluminal myoepithelial differentiated cells. Both tumors have a noticeable tendency to infiltrate around nerves. ACC is a clinically and pathologically well-defined entity which is characterized by the persistent, relentless growth with late metastasis. It occurs primarily in the major salivary glands and relatively frequent occurrence in the intraoral accessory glands particularly the palate. They exhibit cribriform, tubular and solid growth pattern having hyperchromatic and angulated nuclei as well as prominent perineural invasion. PAC arise in the minor salivary gland with a predilection for intraoral sites and exhibit wide variety of growth patterns within a single tumor including solid, glandular, tubular, trabecular, cribriform and single-file pattern. They are characterized by bland, uniform nuclei with lower recurrence rate and rarely metastasis along with prominent neurotropism.

CD117 (C-Kit proto-oncogene) is a type III receptor tyrosine kinase operating in cell signal transduction and are normally expressed in several cell types like hematopoietic stem cells, mast cells, interstitial cells of Cajal, melanocytes, basal cells of skin, breast epithelial cells, germ cells, and cells of the central nervous system. KIT is activated (phosphorylated) by binding of its ligand, the stem cell factor. This leads to a phosphorylation cascade ultimately activating various transcription factors in different cell types. Such activation regulates apoptosis, cell differentiation, proliferation, chemotaxis and cell adhesion. Alteration in the KIT expression is seen in a variety of neoplasms such as mastocytosis, gastrointestinal stromal cell tumours, germ cell tumours, neuroblastomas, gliomas etc. The aim of the present study was to evaluate and compare the immunohistochemical expression of C-Kit (CD117) in differentiating adenoid cystic carcinoma and polymorphous adenocarcinoma.

MATERIAL AND METHODS

A retrospective study was conducted on 20 formalin-fixed, paraffin-embedded tissue blocks, including 15 cases of Adenoid Cystic Carcinoma (5 cases for each pattern) and 5 cases of Polymorphous Adenocarcinoma histopathologically diagnosed using hematoxylin and eosin. All the cases were

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DOI: http://dx.doi.org/10.21276/ijcmr.2020.7.11.7
Evaluation of C-kit immunoreactivity: C-kit immunostaining was evaluated by a semi-quantitative scoring system as:

a) Percentage of C-kit immunoreactivity; b) Intensity of staining

In each section, five high power light microscopic fields were randomly selected. Two observers individually noted the percentage of C-kit positivity in each field and the region of staining was scored as follows:

- Score 0 - no staining of cells in any microscopic field
- Score 1+ - less than 25% of tissue stained positive
- Score 2+ - between 25% and 50% of tissue stained positive
- Score 3+ - between 50% and 75% of tissue stained positive
- Score 4+ - more than 75% of tissue stained positive

The intensity scores were recorded by comparing it with the percentage of C-kit positivity in each field and the region of staining to eliminate any subjective bias. C-Kit expression was determined on the basis of localization, intensity and area of stained cells.

**RESULTS**

In the present study, majority of the patients were females (65%) and rest were males (35%). A good interobserver reliability was found on applying Cronbach’s alpha reliability test to the observations obtained from all two observers for the determination of percentage of C-kit immunoreactivity and intensity of C-kit staining (Table 1).

**Evaluation of C-kit immunostaining:** Dense brown membranous and cytoplasmic c-kit staining patterns of the tumor cells were regarded as positive for antibody. C-kit was expressed in luminal cells of the tubular and cribriform types whereas all the neoplastic cells in solid ACC exhibit C-kit immunostaining (Figure 1A, 1B & 1C). Majority of the cases of PAC revealed absence of C-kit immunostaining (Figure 1D).

**Percentage of C-kit immunoreactivity:** In cribriform and tubular pattern ACC, 40% and 60% of the cases revealed score 3+ and score 4+ respectively but in solid pattern ACC, 100% of the cases showed score 4+. In PAC, 80% and 20% of the cases revealed score 0 and score 1+ respectively. The p-value was found to be statistically significant (Table 2).

**Intensity of C-kit immunostaining:** In cribriform pattern ACC, 40% and 60% of the cases revealed score 2 and score 3 respectively whereas in tubular pattern ACC, 20%, 40% and 60% of the cases revealed score 2, score 3 and score 4 respectively.
and 40% of the cases showed score 1, score 2 and score 3 respectively. In solid pattern ACC, 20%. 60% and 20% of the cases revealed 1, score 2 and score 3 respectively but 60% and 40% of the cases of PAC showed score 0 and score 1 respectively. The p-value was found to be statistically significant (Table 3).

**DISCUSSION**

The C-kit proto-oncogene protein (a transmembrane receptor Type-III tyrosine kinase) on binding to its ligand, stem cell factor initiates a signal cascade which contributes to the growth and differentiation of multiple hematopoietic lineages. It demonstrates structural homology to the receptors of platelet-derived growth factor, macrophage colony stimulating factor. Distinguishing PAC and ACC on H&E morphology alone can be a difficult work especially if in case of biopsies dealing with minor salivary glands. Prognostic difference of the two is sufficiently different thus distinguishing them becomes an important task of the pathologist.

Various studies have been attempted to distinguish ACC from PAC with the help of various antibodies to GFAP, vimentin, S-100 protein, Ki-67, α-smooth muscle actin, muscle specific actin, cytokeratins, c-kit, bel-2, cadherins and CD43. No single antibody has yet been identified that can unambiguously be used in the differentation of ACC and PAC.4, 11 The present study was done to determine and compare the immunohistochemical expression of C-Kit (CD117) in differentiating adenoid cystic carcinoma and polymorphous adenocarcinoma.

In the current study, C-kit percentage was greater in solid pattern ACC followed by cribriform and tubular pattern ACC with a statistically significant p-value. Only 20% of the cases of polymorphous adenocarcinoma revealed percentage of c-kit reactivity. The intensity of c-kit was significantly greater in cribriform pattern ACC followed by tubular and solid pattern ACC. Only 40% of the cases of polymorphous adenocarcinoma showed mild C-kit intensity. These results were in accordance the studies carried out by Andreadis D et al, Meer S et al, Beltran D et al and Epivatianos A et al. 8, 13, 15-16 This signifies that strong expression of C-kit immunoreactivity in adenoid cystic carcinoma as compared to polymorphous adenocarcinoma.

**CONCLUSION**

The distinction between ACC and PAC is important since the clinical course and prognostic significance differ. It is imperative that immunohistochemical stains can be used as an adjuvant in histological-based diagnosis so that simple, accurate, reliable, and reproducible results can be assessed. C-kit can aid in the differential diagnosis of lesion presenting...
a morphological confusion between ACC and PAC. However, the percentage of the C-Kit immunoreactivity and the staining intensity are considered to be an important factor in distinguishing ACC and PAC.

REFERENCES


